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Metabolically Stable Neurotensin (8-13) Analogs as Potential Therapeutic Agents

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A wide range of pharmacological effects have been attributed to the tridecapeptide neurotensin (NT). Two important aspects of neurotensin actions on the central nervous system are its analgesic properties[1] and its possible involvement in the etiology of schizophrenia.[2] The C-terminal hexapeptide fragment of neurotensin (NT(8-13)) has been shown to retain much of the activity found in the native peptide. Indeed NT or NT(8-13) have been shown to possess activity in preclinical antinociceptive tests and in animal behavioral tests predictive of antipsychotic efficacy.[3] NT(8-13) is metabolically unstable and this would limit its use as a therapeutic agent. Studies of the catabolism of NT(8-13) in various brain regions have revealed several key amide bonds which are most susceptible to proteolytic degradation.[4]

Substitution of various unnatural amino acids into NT(8-13) has produced analogs of increased metabolic stability.[5] Some of these analogs when administered systemically have been reported to produce effects which appear to be mediated through central neurotensin receptors. Analogs have been prepared with the goal of understanding the factors necessary for NT receptor binding and agonist activity. The question of whether such agents are indeed crossing the blood brain barrier will also be considered.

1. Bradley, V. Clineschmidt, B.; McGuffin, J.; Bunting, P. *Eur. J. Pharmacol.* **1979**, *54*, 129.

2. Garver D.; Bissette, G.; Yao, J.; Nemeroff, C. *Am J. Psychiatry* **1991**, *148*, 484

3. Ervin, G.; Birkemo, L.; Nemeroff, C.; Prange A. Jr.*Nature* **1981**, *29*, 73

4. Davis, T.P.; Gillespie, T.J.; Konings, P.N.M. *J.Neurochem.* **1992**, *58*, 608

5. Tsuchiya, Y.; Sasaki, A.; Yoshino, H.; Karibe, N.; Sugimoto, H.; Kubota, A.; Kosasa, M.; Araki, S.; Uchikoshi, K.; Yamanishi, Y.; Machida, R.; Yamatsu, K. 200th American Chemical Society National Meeting Wasington D.C. 1990